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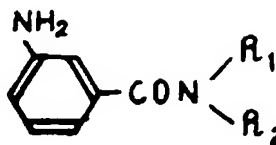
(54) BLOOD SUGAR LEVEL DEPRESSING AGENT

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(57) Abstract:

PURPOSE: To provide a blood sugar level depressing agent containing a VSHF benzamide derivative as an active component.

CONSTITUTION: An agent containing the compound of formula [R₁ and R₂ are H, alkyl, (substituted) aralkyl, or (substituted) phenyl] as an active component. The compound of formula has excellent insulin biosynthesis promoting activity and blood sugar level depressing activity. It is effective at a dose of 0.1W100mg/kg for man, and maintains the activity for ≥ 24 hr by the administration of 0.1W100mg/kg, once a day. The compound of formula can be prepared easily e.g. by reducing the corresponding m-nitrobenzoic acid amide by conventional method.



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⑩ 特許出願公開

⑫ 公開特許公報 (A)

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⑪ Int. Cl.³
A 61 K 31/13
31/165

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庁内整理番号
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発明の数 1
審査請求 未請求

(全 4 頁)

⑭ 血糖降下剤

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⑮ 特 願 昭55-93853

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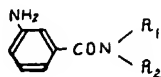
明 細 書

1. 発明の名称

血糖降下剤

2. 特許請求の範囲

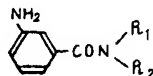
一般式



(式中、 R_1 及び R_2 は同一又は異って、水素原子、直鎖・分岐鎖・環状アルキル基、核に置換基を有し得るアラルキル基又は置換基を有し得るフェニル基を示す。) で表わされる化合物を有効成分とする血糖降下剤。

3. 発明の詳細な説明

本発明は、次の一般式



[1]

(式中、 R_1 及び R_2 は同一又は異って、水素原子、直鎖・分岐鎖・環状アルキル基、核に置換基を有

し得るアラルキル基又は置換基を有し得るフェニル基を示す。) で表わされる化合物を有効成分とする血糖降下剤の発明である。

上式〔1〕で表わされる化合物の中には、公知の化合物が含まれるが、それらの記載されている先行文献には血糖降下作用ないしそれを示唆する薬理作用は全く記載されていない。

上式〔1〕で表わされる本発明の化合物は、例えば、以下の参考例に示すように、対応するメタニトロ安息香酸アミド類を常法により還元することにより容易に得ることができる。

参考例。

イソプロピルアミン6g、トリエチルアミン15ml及びアセトン200mlの混合溶液に、氷冷攪拌下、メタニトロベンゾイルクロライド18.6gを徐々に加える。同温度で30分、次いで室温で1時間攪拌後反応溶液を1ℓの水に注ぎ、析出する結晶を回収し、水洗後再結晶して無色針状晶のメタニトロ-N-イソプロピルベンズアミド(融点131~132℃)18.7gを得た。この5.2

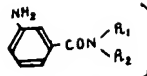
9、10%パラジウム-炭素0.5g及びエタノール100mlの混液に水素を通じ、常法により接触還元する。計算量の水素を吸収後触媒を除去し、反応液を減圧濃縮し、残渣をエタノールより再結晶して無色針状晶のメタアミノ-N-イソプロピルベンズアミド(化合物1)4.1gを得た。融点148~149℃。




元素分析値 分子式 $C_{10}H_{14}N_2O$ として













	C	H	N
理論値(%)	67.38	7.92	15.72
実測値(%)	67.35	7.94	15.69

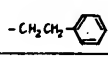
上記と同様にして表1の化合物を得た。

なお、化合物25、27及び29は油状で得られたので表中にハイマスペクトルの値を、欄外にNMRの値を記載した。

表-1 

化合物 No.	置換基及び置換位置		分子式	融点 (℃)	収率 (%)	元素分析値					
	R ₁	R ₂				理論値(%)			実測値(%)		
						O	H	N	O	H	N
2	H	H	$C_7H_9N_2O$	77~78	81	61.75	5.92	20.58	61.71	5.96	20.55
3	"	CH ₃	$C_8H_{10}N_2O$	121~122	85	63.98	6.71	18.65	63.92	6.68	18.69
4	"	C ₂ H ₅	$C_9H_{12}N_2O$	70~71	76	65.83	7.37	17.06	65.72	7.28	17.19
5	"	n-C ₃ H ₇	$C_{10}H_{14}N_2O$	57~58	78	67.38	7.92	15.72	67.25	7.88	15.64
6	"	n-C ₄ H ₉	$C_{11}H_{16}N_2O$	112~113	75	68.72	8.39	14.57	68.70	8.37	14.50
7	"	sec-C ₄ H ₉	"	109~111	74	"			68.67	8.44	14.65
8	"	t-C ₄ H ₉	"	126~127	79	"			68.69	8.36	14.51
9	"	i-C ₄ H ₉	"	87~89	76	"			68.75	8.46	14.62
10	"		$C_{13}H_{19}N_2O$	147~148	84	71.52	8.31	12.83	71.58	8.35	12.76
11	"		$C_{13}H_{13}N_2O$	132~133	86	73.56	5.70	13.20	73.50	5.67	13.26
12	"		$C_{14}H_{15}N_2O$	88~89	84	74.31	6.24	12.38	74.24	6.20	13.45

No	置換基及び置換位置		分子式	融点 (°C)	収率 (%)	元素分析値					
	R ₁	R ₂				理論値(%)			実測値(%)		
						O	H	N	O	H	N
13	H		C ₁₅ H ₁₆ N ₂ O ₃	83~84	76	66.16	5.92	10.29	65.98	5.88	10.35
14	"		C ₁₄ H ₁₃ N ₃ O ₂	180~182	56	65.87	5.13	16.46	65.75	5.18	16.55
15	"		"	135~136	59	"	"	"	65.79	5.10	16.52
16	"		"	223~226	68	"	"	"	65.81	5.07	16.53
17	"		C ₁₃ H ₁₃ N ₃ O	151~153	79	68.70	5.77	18.49	68.64	5.79	18.43
18	"		"	130~131	71	"	"	"	68.77	5.70	18.53
19	"		"	150~151	74	"	"	"	68.75	5.67	18.42
20	"		C ₁₄ H ₁₂ N ₂ O ₃	231~233	59	65.62	4.72	10.93	65.71	4.66	11.02
21	"		C ₁₄ H ₁₄ N ₂ O	96~97	73	74.31	6.24	12.38	74.25	6.19	12.49
22	"		C ₁₅ H ₁₆ N ₂ O	94~95	80	74.97	6.71	11.66	74.92	6.75	11.61
23	"		C ₁₅ H ₁₆ N ₂ O ₂	109~110	79	70.29	6.29	10.93	70.34	6.32	10.89
24	"		C ₁₄ H ₁₃ ON ₂ O	131~132	67	64.49	5.03	10.75	64.42	5.00	10.79

No	置換基及び置換位置		分子式	融点 (°C)	収率 (%)	元素分析値					
	R ₁	R ₂				理論値(%)			実測値(%)		
						O	H	N	O	H	N
25	H		C ₁₅ H ₁₆ N ₂ O	oil	62	ハイマススペクトル 24.01259			(#1) 24.01246		
26	CH ₃	CH ₃	C ₉ H ₁₂ N ₂ O	87~88	82	65.83	7.37	17.06	65.78	7.41	17.12
27	n-C ₃ H ₇	n-C ₃ H ₇	C ₁₃ H ₂₀ N ₂ O	oil	76	ハイマススペクトル 22.01571			(#2) 22.01580		
28	i-C ₃ H ₇	i-C ₃ H ₇	"	179~180	80	70.87	9.15	12.72	70.79	9.15	12.78
29	n-C ₄ H ₉	n-C ₄ H ₉	C ₁₅ H ₂₄ N ₂ O	oil	74	ハイマススペクトル 24.81883			(#3) 24.81875		
30	i-C ₄ H ₉	i-C ₄ H ₉	"	85~86	79	72.54	9.74	11.28	72.48	9.79	11.34

*1: NMR (CDCl₃) δ: 7.55~6.40 (10H, aromatic-H, -CONH-), 3.75 (2H, s, -NH₂),
3.45 (2H, t, J=6Hz, -CH₂-), 2.75 (2H, t, J=6Hz, -CH₂-)

*2: NMR (CDCl₃) δ: 7.35~6.50 (4H, aromatic-H), 3.90 (2H, s, -NH₂), 3.30 (4H,
t, J=6Hz, (-CH₂CH₂CH₂)×2), 1.60 (4H, sextet, J=6Hz, (-
-OH₂CH₂CH₂)×2), 0.85 (6H, t, J=6Hz, (-OH₂CH₂CH₂)×2)

*3: NMR (CDCl₃) δ: 7.15~6.40 (4H, aromatic-H), 4.00 (2H, s, -NH₂), 3.30 (4H,
br, (-CH₂CH₂CH₂CH₂)×2), 1.40 (8H, br, (-CH₂CH₂CH₂CH₂)
×2), 0.90 (6H, br, (-CH₂CH₂CH₂CH₂)×2)

このようにして得られる本発明の化合物は、優れたインスリン生合成促進作用及び血糖降下作用を有し、ヒトに対しては0.1~100mg/kgで有効で、1日1回0.1~100mg/kgの投与で24時間以上その効力を持続する。

投与に際しては、通常の製剤化に用いられる慣用手段により所望の剤形に成形された製剤が用いられる。

実施例 1.

1群5匹の5週令DDY系マウス(雄、体重25~30g)を16時間絶食後、本発明化合物(200mg/kg)の水溶液又はけん濁液を経口投与し、20分後にストレプトゾトシン200mg/kgを静脈内に投与した。24時間後に心臓から採血し、グルコースオキシダーゼ法により血中糖量を、また、二抗体法により血しょうインスリン量を測定した。測定結果を表2に例示する。

なお、表中の化合物番号は参考例の化合物番号に対応している。

投与化合物	血糖値 (mg/dl) mean ± S. E. M.	血しょうインスリン (μU/dl) mean ± S. E. M.
正常マウス	157 ± 6	199 ± 40
なし(対照)	386 ± 21	43 ± 25
1	224 ± 19***	176 ± 37*
2	157 ± 16***	153 ± 46
3	260 ± 33*	213 ± 48*
4	248 ± 47*	192 ± 54
10	263 ± 36*	201 ± 38*
12	265 ± 32*	253 ± 56*
18	166 ± 35***	190 ± 51*
21	150 ± 6***	224 ± 30**
24	193 ± 41**	173 ± 63
25	210 ± 39**	184 ± 48*
26	267 ± 53	220 ± 37**

*: P<0.05 **: P<0.01 ***: P<0.001

実施例 2

メタアミノベンズアミド(化合物2) 100 部
リン酸水素カルシウム 58.5 部
結晶セルロース 50 部
コーンスターチ 40 部
ステアリン酸カルシウム 1.5 部

これらをよく混合し、常法により1錠250mgに打錠(有効成分100mg含有)し、血糖降下用錠剤として用いる。

実施例 3

メタアミノ-N-ベンジルベンズアミド(化合物21)の40%水溶液を調製し、1アンプルに2mlずつ封入し、滅菌して血糖降下用注射剤として用いる。

出願人 中外製薬株式会社

代理人 安 藤 憲 章

第1頁の続き

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DRAFT TRANSLATION from
RISING SUN COMMUNICATIONS LTD.

(Incorporating Rotha Fullford Leopold of Canberra, Australia)

40 Bowling Green Lane, London EC1R 0NE

JAPANESE PATENT APPLICATION

No. J57-021320

A HYPOGLYCEMIC AGENT

(21) Filing no.: 55-93853

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Examination request: not yet made

Number of Invention: 1

(Total 4 pages)

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31/165		6408-4C

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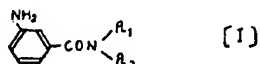
Specification

1. Title of Invention

A hypoglycemic agent.

2. Patent Claims

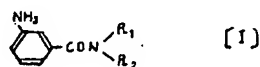
A hypoglycemic agent containing as effective component a compound represented by general formula



(wherein, R₁ and R₂ may be the same or different and denote a hydrogen atom, a straight-chain, branched-chain or cyclic alkyl group, an aralkyl group which can have a substituent in the nucleus, or a phenyl group which may be substituted).

3. Detailed explanation of the invention

This invention is a hypoglycemic agent containing as effective component a compound represented by general formula



(wherein, R₁ and R₂ may be the same or different and denote a hydrogen atom, a straight-chain, branched-chain or cyclic alkyl group, an aralkyl group which can have a substituent in the nucleus, or a phenyl group which may be substituted).

Among the compounds represented by aforesaid formula [I], a well known compounds are included, however, hypoglycemic action or a pharmacological action that suggests this are not described whatsoever in the prior publications describing those compounds.

The compounds represented by aforesaid formula [I] can be easily obtained for example by reduction by conventional method of corresponding meta-nitrobenzoic acid amide species as shown in the Reference Example below.

Reference Example

Into a mixed solution of 6 g isopropylamine, 15 ml triethylamine and 200 ml acetone was gradually added 18.6 g meta-nitrobenzoyl chloride under ice cooling and stirring. the mixture was stirred at the same temperature for 30 minutes and then at room temperature for one hour, thereafter, the reaction liquor was discharged into 1 litre of water, precipitated crystals were recovered by

filtration, washed with water, thereafter recrystallised, and meta-nitro-N-isopropylbenzamide (m.p. 131-132°C) 18.7 g was thereby obtained as colourless acicular crystals. Hydrogen was passed through a mixed liquor of 5.2 g of said amide, 0.5 g of 10 % palladium-carbon and 100 ml ethanol, and catalytic reduction was carried out by conventional method. After theoretical quantity hydrogen was absorbed, catalyst was eliminated, the reaction liquor was concentrated under reduced pressure, the residue was recrystallised from ethanol, and thereby meta-amino-N-isopropyl benzamide (compound 1) 4.1 g was obtained as colourless acicular crystals. m.p. 148-149°C.

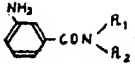
Elemental analysis: as molecular formula $C_{10}H_{14}N_2O$




	C	H	N
Calculated values (%)	67.38	7.92	15.72
Measured values (%)	67.35	7.94	15.69













Compounds of Table 1 were obtained in the same way as above.

wherein, compounds 25, 27 and 29 were obtained as oily substances, the value of high mass spectra are shown in the Table and the NMR values are shown below the Table.

Table 1


[1]

Comp. No.	Substituent and position		Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value					
	R ₁	R ₂				Calc. (%)			Measured (%)		
						C	H	N	C	H	N
2	H	H	C ₇ H ₉ N ₂ O	77~78	81	61.75	5.92	20.58	61.71	5.96	20.55
3	"	OH ₂	C ₈ H ₁₀ N ₂ O	121~122	85	63.98	6.71	18.65	63.92	6.68	18.69
4	"	O ₂ H ₂	C ₉ H ₁₂ N ₂ O	70~71	76	65.83	7.37	17.06	65.72	7.28	17.19
5	"	n-C ₃ H ₇	C ₁₀ H ₁₄ N ₂ O	57~58	78	67.38	7.92	15.72	67.25	7.88	15.64
6	"	n-C ₄ H ₉	C ₁₁ H ₁₆ N ₂ O	112~113	75	68.72	8.39	14.57	68.70	8.37	14.50
7	"	sec-C ₄ H ₉	"	109~111	74	"	"	"	68.67	8.44	14.65
8	"	i-C ₄ H ₉	"	126~127	79	"	"	"	68.69	8.36	14.51
9	"	t-C ₄ H ₉	"	87~89	76	"	"	"	68.75	8.46	14.62
10	"		C ₁₃ H ₁₈ N ₂ O	147~148	84	71.52	8.31	12.89	71.58	8.35	12.76
11	"		C ₁₃ H ₁₇ N ₂ O	132~133	86	73.56	5.70	13.20	73.50	5.67	13.26
12	"		C ₁₄ H ₁₄ N ₂ O	88~89	84	74.31	6.24	12.38	74.24	6.20	13.45

Comp. No.	Substituent and position		Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value					
	R ₁	R ₂				Calc. (%)			Measured (%)		
						C	H	N	C	H	N
13	H		C ₁₅ H ₁₆ N ₂ O ₂	83~84	76	66.16	5.92	10.29	65.98	5.88	10.36
14	"		C ₁₄ H ₁₃ N ₂ O ₂	180~182	56	65.87	5.13	16.46	65.75	5.18	16.55
15	"		"	135~136	69	"	"	"	65.79	5.10	16.52
16	"		"	223~226	68	"	"	"	65.81	5.07	16.53
17	"		C ₁₃ H ₁₂ N ₂ O	151~153	79	68.70	5.77	18.49	68.64	5.79	18.43
18	"		"	130~131	71	"	"	"	68.77	5.70	18.53
19	"		"	150~151	74	"	"	"	68.75	5.67	18.42
20	"		C ₁₄ H ₁₂ N ₂ O ₂	231~233	59	65.62	4.72	10.93	65.71	4.66	11.02
21	"	-CH ₂ - 	C ₁₄ H ₁₄ N ₂ O	96~97	73	74.31	6.24	12.38	74.25	6.19	12.49
22	"	-CH ₂ - 	C ₁₅ H ₁₆ N ₂ O	94~95	80	74.97	6.71	11.66	74.92	6.75	11.61
23	"	-CH ₂ - 	C ₁₅ H ₁₆ N ₂ O ₂	109~110	79	70.29	6.29	10.93	70.34	6.32	10.89
24	"	-CH ₂ - 	C ₁₄ H ₁₃ ON ₂ O	131~132	67	64.49	5.02	10.75	64.42	5.00	10.79

Comp. No.	Substituent and position		Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value					
	R ₁	R ₂				Calc. (%)			Measured (%)		
						C	H	N	C	H	N
25	H		C ₁₈ H ₁₈ N ₂ O	oil	62	ハイマススペクトル 240.1259			(#1) 240.1246		
26	OH ₃	OH ₃	C ₉ H ₁₂ N ₂ O	87~88	82	65.83	7.37	17.06	65.78	7.41	17.12
27	n-C ₃ H ₇	n-C ₃ H ₇	C ₁₃ H ₂₀ N ₂ O	oil	76	ハイマススペクトル 220.1571			(#2) 220.1580		
28	i-C ₃ H ₇	i-C ₃ H ₇	"	179~180	80	70.87	9.15	12.72	70.79	9.15	12.78
29	n-C ₄ H ₉	n-C ₄ H ₉	C ₁₃ H ₂₄ N ₂ O	oil	74	ハイマススペクトル 248.1883			(#3) 248.1875		
30	i-C ₄ H ₉	i-C ₄ H ₉	"	85~86	79	72.54	9.74	11.28	72.48	9.79	11.34

1 : NMR (CDCl₃) δ : 7.55~6.40 (10H, aromatic-H, -CONH-), 3.75 (2H, s, -NH₂),
3.45 (2H, t, J=6Hz, -OH₂-), 2.75 (2H, t, J=6Hz, -CH₂-)

2 : NMR (ODCl₃) δ : 7.35~6.50 (4H, aromatic-H), 3.90 (2H, s, -NH₂), 3.30 (4H,
t, J=6Hz, (-CH₂OH₂CH₂)×2), 1.60 (4H, sextet, J=6Hz, (-CH₂CH₂CH₂)×2), 0.85 (6H, t, J=6Hz, (-OH₂CH₂CH₂)×2)

3 : NMR (ODCl₃) δ : 7.15~6.40 (4H, aromatic-H), 4.00 (2H, s, -NH₂), 3.30 (4H,
br, (-CH₂OH₂CH₂CH₂)×2), 1.40 (8H, br, (-CH₂OH₂CH₂CH₂)×2), 0.90 (6H, br, (-CH₂CH₂OH₂CH₂)×2)

The compounds of this invention obtained in this way have excellent insulin biosynthesis promotion action and hypoglycemic action, and are useful at 0.1-100 mg/kg with respect to human, and the effect thereof can be sustained for 24 hours or more by the administration of 0.1-100 mg/kg once a day.

For administration, preparations formed into desired agent form by conventional means used for normal formulation method are used.

Example 1

5-week-old DDY mice (males, body weight 25-30 g) comprising 5 animals per group were fasted for 16 hours, thereafter, aqueous solution or suspension of compounds of this invention (200 mg/kg) was orally administered, and 20 minutes later, streptozotocin 200 mg/kg was intravenously administered. Blood was collected from the heart on 24 hours later, blood sugar quantity was measured by glucose oxidase method and the plasma insulin quantity was measured by two antibody method. The measurement results are shown in Table 2.

Wherein, the compound number in the Table corresponds to the compound number of Reference Example.

Table 2

Administered compound	Blood glucose (mg/dl) mean \pm S.E.M.	Plasma Insulin (μ U/ml) mean \pm S.E.M.
Normal mouse	157 \pm 6	199 \pm 40
None (control)	386 \pm 21	43 \pm 25
1	224 \pm 19 ***	176 \pm 37 *
2	157 \pm 16 ***	153 \pm 46
3	260 \pm 33 *	213 \pm 48 *
4	248 \pm 47 *	192 \pm 54
10	263 \pm 36 *	201 \pm 38 *
12	265 \pm 32 *	253 \pm 56 *
18	166 \pm 35 ***	190 \pm 51 *
21	150 \pm 6 ***	224 \pm 30 ***
24	193 \pm 41 **	173 \pm 63
25	210 \pm 39 **	184 \pm 48 *
26	267 \pm 53	220 \pm 37 **

*: P < 0.05, **: P < 0.01, ***: P < 0.001

Example 2

meta-aminobenzamide (compound 2)	100 pts.
calcium hydrogenphosphate	58.5 pts.
crystalline cellulose	50 pts.
corn starch	40 pts.
calcium stearate	1.5 pts.

Above components were thoroughly mixed, and tablets, 250 mg per tablet (containing 100 mg effective component) was formed by conventional method. This is used as a hypoglycemic agent.

Example 3

A 40 % aqueous solution of meta-aminobenzylbenzamide (compound 21) was prepared, and 2 ml each thereof was sealed into ampoules and sterilised. This is used as a hypoglycemic injection.

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